REMARKS

Claims 1-2, 4-13, 16-20, 22-37, 41-43 and 45-47 are pending in the subject application. Applicants have amended claims 1, 5, 7, 9-10, 12, 18, 25, 27-30, 35-37, and 43. Support for these amendments may be found inter alia in the specification as follows: for the term "VP3" recited in claim 5: page 12, lines 9-10 and page 21, lines 10-14; and for the term "nucleoprotein" recited in claims 1, 18 and 35: page 34, line 12. The remaining changes to the claims merely introduce minor grammatical and format changes. In making these amendments, applicants neither concede the correctness of the Examiner's rejections, nor abandon their right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. These amendments do not involve any issue of new matter. Therefore, entry of these amendments is respectfully requested such that claims 1-2, 4-13, 16-20, 22-37, 41-43 and 45-47 will still be pending.

Formalities

Applicants acknowledge the Examiner's statement that the request filed on October 22, 2002 for a Continued Prosecution Application (CPA) under 37 CFR §1.53(d) based on parent Application No. 09/068,293 is acceptable and a CPA has been established.

The Examiner also withdrew the following outstanding rejections: the rejection of claims 1, 2, 4-13, 16-20, 22-28 and 43 under 35 U.S.C. §112, second paragraph; the rejection of claims 1, 2, 4, and 5 under 35 U.S.C. §102(b) over Colomar et al.; the rejection of the claims 1, 2, 4-13, 16-20, 22-37, 41-43 and 45-47 under 35 U.S.C. §103 over Colomar et al. in view of Christensen et al., Carswell et al., Oppenheim et al., (J. Virol. Vol. 66, 1992) and U.S. Pat. No. 5,863,541. Applicants acknowledge the withdrawal of these rejections.

Drawings

The Examiner stated that the proposed drawing correction and/or the proposed substitute sheets of drawings, filed on December 16, 2002 have been approved. The Examiner stated that a proper drawing correction or corrected drawings are required in reply to this office action to avoid abandonment of the application. The Examiner stated that the correction to the drawings will not be held in abeyance.

In response, applicants respectfully traverse. Contrary to the Examiner's statement, applicants point out that the Communication Forwarding Formal Drawing which applicants submitted to the United States Patent and Trademark Office on December 16, 2002 included one (1) sheet of a **new, corrected formal drawing** which included Figures 3A and 3C in response to the August 20, 1998 Notice of Draftperson's Patent Drawing Review, **not a proposed drawing correction.** Nevertheless, without

Nevertheless, without conceding the correctness of the Examiner's statement but in order to expedite prosecution of the subject application, applicants attach hereto as **Exhibit A** one (1) additional sheet of a new, corrected formal drawing which includes Figures 3A and 3C as required by the August 20, 1998 Notice of Draftperson's Patent Drawing Review.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claim 5 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated that claim 5 recites the capsid protein "VPS". The Examiner stated that capsid protein "VPS" is not described in the originally filed claims or specification. Therefore, the Examiner stated that the amendment of claim 5 to add the limitation where the capsid protein may be "VPS" constitutes new matter.

In response, applicants respectfully traverse. Nevertheless, without conceding the correctness of the Examiner's rejection but to expedite prosecution of the subject application, applicants have hereinabove amended claim 5 such that it no longer recites "VPS" but instead now recites "VP3", which is described in the specification. Therefore, applicants

respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1, 2, 4-13, 19, 25, 27, 29-34, 36, 37 and 43 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner stated that there is insufficient antecedent basis for the following limitations: claim 1: the limitation "the infectivity" in lines 28 and 29, and "the packaged recombinant nucleic acid" in lines 28-29; claim 5: the limitation "in said cell" in line 4; claim 9: the limitation "in said mammalian cell" in line 6; claim 10: the limitation "in said cell" in lines 4 and 10, and "in said mammalian cell" in line 15; claim 12: the limitation "said constituent is an exogenous protein or peptide" in line 2, and "in said cell" in line 4; claim 25: the limitation "in said cell" in line 4; claim 27: the limitation "said exogenous protein" in line 5; claim 28: the limitation "in said cell" or "in said mammalian cell" in lines 5, 12 and 16; claim 29: the limitation "said purified exogenous protein" in lines 11-12; claim 30: the limitation "any non-packaged protein" in lines 2-3; claim 36: the limitation "non packaged DNA" in liens 2-3; claim 37: the limitation "the mixture" in line 3; and

claim 43: the limitation "purified exogenous protein or peptide" in line 4.

In response, applicants respectfully traverse the Examiner=s rejections with respect to claims 1, 2, 4-13, 19, 25, 27, 29-34, 36, 37 and 43. Nevertheless, without conceding the correctness of the Examiner's rejections but to expedite prosecution of the subject application, applicants have hereinabove amended claims 1, 2, 4-13, 19, 25, 27, 29-34, 36, 37 and 43 to address the Examiner's rejections. Applicants contend that these amendments obviate the above rejections. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these grounds of rejection.

Claim Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 2, 4-11, 13, 16-20, 22-28, 35-37, 41-43, 45 and 46 under 35 U.S.C. §102(b) as allegedly being anticipated by WO92/16638 (Hellwig et al.).

The Examiner stated that Hellwig et al. teach at the abstract, pages 6-8, 17-20, 24 (section II.E.) and 25-26 (section V), an infectious particle complex comprising purified SV40 VP1, VP2 and VP3 proteins and a purified recombinant nucleic acid constituent packaged therein, and a method for making the infectious particle complex (citing page 6, lines 5-32). The Examiner stated that the infectious particle may be used to

infect a mammalian cell. The Examiner stated that the particle may be treated with nuclease digestion (citing page 2, lines 5-12 and page 5, lines 10-16). The Examiner stated that the nucleic acid may encode a protein, and may be expressed in the cell, or may be an antisense nucleic acid (DNA or RNA), or may encode an antisense nucleic acid (citing page 17). The Examiner stated that the encoded protein may be expressed in the cell. The Examiner stated that the encoded protein may replace, compliment or correct a protein which is endogenous to the cell (citing page 18, lines 1-6). The Examiner stated that the complex may be in a pharmaceutically acceptable carrier (citing pages 17-20).

In response, applicants respectfully traverse the Examiner=s rejection. Briefly, claims 1, 2, 4-11, 13, 16-20, 22-28, 35-37, 41-43, 45 and 46 provide an infectious particle complex comprising one or more SV40 capsid proteins and a purified recombinant nucleic acid constituent which is <u>not a nucleoprotein</u> [emphasis added]. Without conceding the correctness of the Examiner's rejection but in order to expedite prosecution of the subject application, applicants have hereinabove amended claims 1, 18 and 35 to reflect that the infectious particle complex of applicants' invention does not include a nucleoprotein.

There are several critical differences between Hellwig et al. and the present invention. A key element in Hellwig et al. is

the packaging of DNA complexed in nucleosomes, i.e. a histone-containing nucleoprotein complex of a similar size to that of the virus (see page 7, lines 15-17 of Hellwig et al.). The present invention relates to the packaging of a purified recombinant nucleic acid constituent, **without** histones [emphasis added].

In addition, as can be seen in the description and in claim 14 of Hellwig et al., the transduction vehicle (which the Examiner considers equivalent to the infectious particle complex of the invention) comprises a capsid and a nucleoprotein complex. Therefore, the infectious particle of applicants' invention is different from the transduction vehicle of Hellwig et al., since it does not contain a nucleoprotein complex. Thus, amongst other differences, the absence of histones renders the constructs of the invention novel over Hellwig et al.

With regards to the method, in the present application, the semi-purified capsid proteins are prepared from isolated nuclei, by extracting them at pH 7.9 at high salt concentration (0.4M NaCl). Under these conditions the cellular chromatin (DNA and histones) remains in the nuclear pellet, and is therefore not contained in the nuclear extracts. Thus, histones are excluded from the process of the invention at all stages, and also from the final, *in vitro* packaged constructs. As recited in the method claims (e.g., claims 18 and 35), the capsid protein/s are brought into contact with the purified recombinant nucleic acid component.

In the process of Hellwig et al., the capsid proteins are brought into contact with a nucleoprotein complex, not with a purified recombinant nucleic acid constituent. Moreover, Hellwig et al. describe the assembly of the nucleoprotein molecule, prior to its encapsidation (page 16). The DNA is mixed with histones. In the method of the present invention, no treatment of the purified nucleic acid is necessary prior to contacting the capsid protein/s. The present specification addresses this point at lines 8-10, page 33 (packaging of naked DNA as compared to nucleosomes). Therefore, the method of the present invention is not anticipated by Hellwig et al.

In view of the above remarks and amendments, applicants maintain that claims 1, 2, 4-11, 13, 16-20, 22-28, 35-37, 41-43, 45 and 46 satisfy the requirements of 35 U.S.C. §102(b) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 12, 29-34 and 47 under 35 U.S.C. §103(a) as allegedly being unpatentable over WO92/16638 (Hellwig et al.) in view of Hong et al.

The Examiner stated that the claims are drawn to a method for the *in vitro* construction of SV40 viruses or pseudoviruses comprising a constituent, where the constituent comprises a

purified exogenous peptide or protein. The Examiner stated that SV40 capsid proteins self assemble *in vitro* in a mixture including the purified exogenous peptide or protein, whereby the purified exogenous peptide or protein is encapsidated into the self assembled SV40 pseudovirus. The Examiner stated that the peptide or protein may replace, compliment or correct a protein which is endogenous to the cell.

The Examiner stated that Hellwig et al. teach the invention as described above in the rejection under 35 U.S.C. §102. The Examiner stated that Hellwig et al. did not teach that a desired protein may be packaged into the virus or pseudovirus.

The Examiner stated that Hong et al. teach at the abstract, and conclusion, a method of encapsidating a non-capsid, non-viral protein in a viral pseudocapsid. The Examiner stated that the viral pseudocapsid is derived from phage T4, which forms an icosahedral capsid.

The Examiner stated that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the infectious particle complex comprising purified SV40 VP1, VP2 and VP3 proteins and a purified recombinant nucleic acid constituent packaged therein, and a method for making the infectious particle complex of Hellwig et al. with the viral capsid used for protecting the exogenous protein of Hong et al. to produce the instant claimed invention because both Hellwig et al. and Hong et al. teach the packaging of non-viral nucleic

acids in self assembled viral capsid proteins to form a virus or pseudovirus. The Examiner stated that one of ordinary skill in the art would have been motivated to modify the teachings of Hellwig et al. with the teachings of Hong et al. (at the abstract) for the expected benefit of packaging of non-viral nucleic acids as well as proteins in pseudovirus capsids which self-assemble to stabilize and protect the encapsidated non-viral nucleic acids and proteins for delivery to the cells of Hellwig et al. Further, the Examiner stated that a person of ordinary skill in the art would have had a reasonable expectation of success in producing the instant claimed invention given the teachings of Hellwig et al. and Hong et al. who demonstrate package of non-viral nucleic acids as well as proteins in pseudovirus capsids which self-assemble to stabilize and protect the encapsidated non-viral nucleic acids and proteins for delivery to cells.

In response to the Examiner=s rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a prima facie case of obviousness against the rejected claims.

Briefly, the rejected claims define an infectious particle complex and method for preparing such infectious particle complex in which the exogenous constituent is an exogenous protein or peptide.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

The references cited against the rejected claims fail to support a prima facie case of obviousness.

As the Examiner stated, Hellwig et al. do not teach the packaging of proteins or peptides. Moreover, as explained above, Hellwig teaches a method which employs nucleoprotein complex, particularly DNA/histone complex as the constituent to be packaged. The exclusion of histones is an essential feature of the present invention, and a major contribution to the inventive step therein. It facilitates packaging of plasmids which are significantly larger than the SV40 genome, and the inclusion of potent regulatory signals.

The present invention facilitates packaging of plasmids of 7-7.4 kb (see Table 3, page 33 of the published PCT application). The inventors have recently shown packaging of 15 and 17 kb plasmids (see Kimchi Sarfaty et al., *Human Gene Therapy*, 14:167-177 (2003), e.g. in the abstract, Fig. 1, Fig. 4 and corresponding text). The space within an SV40 particle limits the packaging size of a nucleoprotein complex to about 5.4kb [Chang, X.B. and

Wilson, J.H., *J. Virol.* 58:393 (1986)]. Therefore, the mere fact that the present inventors demonstrated the packaging of much larger plasmids, in the application as filed and thereafter shows the difference between the constructs of Hellwig et al. and those of the present invention, because it would not have been possible to package a nucleoprotein complex of a size exceeding about 5.4kb, which Hellwig et al., would have been aware of this limitation, suggest to package plasmids of approximately the same size as the native virus (but do not show how to do it). Only because naked DNA is packaged, is it possible to package the very large plasmids shown in Table 3 of the present invention (and subsequent studies).

The exclusion of histones also allows packaging of potent regulatory elements, such as the β-globin locus control region (LCR). As shown in Table 3 of the application, β-globin LCR elements do not adversely effect the efficiency of packaging of naked DNA. In contrast, these elements cause great problems in packaging of nucleoprotein complexes, due to the formation of higher order structures that are not compatible with the nucleosomal condensation, which is required for packaging [Dalyot, N., Regulation of the human β-globin gene and the development of a model for gene therapy of β-thalassemia, Ph.D. Thesis (1991) The Hebrew University of Jerusalem]. The ability to package naked DNA that carries the β-globin LCR demonstrates the difference between the constructs of Hellwig et al. and those of the present invention, because it is not possible to package a nucleoprotein complex that contains the β-globin LCR.

Moreover, the exclusion of histones is most important for gene therapy applications, as it not only allows the packaging and delivery of large plasmids that can carry large genes, but also allows the inclusion of potent regulatory elements. Such potent regulatory elements may be critical for high and properly regulated expression of the transgene (i.e. β-globin), and their inclusion is crucial for gene therapy application of the constructs.

Furthermore, Hellwig et al. is limited to the packaging of DNA only, as a nucleoprotein complex, while the present invention also relates to packaging of RNA and proteins.

Additionally, Hellwig et al. do not teach how to prepare the transduction vehicles claimed therein. Part II D (Example 1) of Hellwig et al. is based on the preparation of polyoma capsid proteins in *E. coli,* as described by Leavitt et al. and Salunke et al. (page 23, lines 25 et seq. of Hellwig et al.). As already discussed in earlier stages of prosecution, polyoma and SV40 are not the same virus. Although they are both members of the papova virus family, there are many differences between them. A major difference that is relevant to this part of the invention is that polyoma capsid proteins VP2 and VP3 lack a DNA binding domain that is present in SV40 VP2 and VP3. Part II E of Example 1 is also not enabling for the production of VP2 and VP3. The studies of Leavitt *et al.* and of Salunke *et al.* describe production of polyoma VP1 only. VP2 and VP3 and

various derivatives of these proteins are insoluble when produced in *E. coli* [Chen *et al.*, *EMBO J.* (1998)], in particular when each is produced alone. The same is true for SV40 VP3 [Shamri, M.Sc. Thesis (in Hebrew) (1998) Hebrew University of Jerusalem]. Thus, it is impossible to obtain functional VP2 and VP3 in bacteria. Following the protocols suggested in Hellwig et al. would result in the production of insoluble protein aggregates. These protein aggregates will not package DNA. Therefore, parts II(D) and II(E) of Example 1 of Hellwig et al., which are key parts of its alleged invention, do not allow one of skill in the art to achieve the promised result. Part V of Example 1 of Hellwig et al. also does not teach assembly of pseudovirions. The protocol is based on the experiments of J.N. Brady *et al.* [*J. Virol.* 32(2):64-647 (1979), see Hellwig et al., page 2, lines 14-15], performed on polyoma virus, and not on SV40, in which no attempt was made to package heterologous DNA. Brady et al. performed a mild disassembly of polyoma, followed by the re-association, with a 10,000-fold loss in activity. Therefore this method would fail to lead to the production of infectious particles carrying heterologous DNA.

Hong et al. describes (a) a novel expression system in *E. coli* and (b) the incorporation of a non-viral protein into a pseudocapsid of bacteriophage T4. The incorporation of the non-viral protein (β-globin in the example described in the article) into the pseudocapsid was achieved by <u>fusing</u> β-globin with a truncated form of the T4 internal protein IPIII, using standard cloning protocols. The resulting fusion protein was efficiently

expressed in *E. coli* and was packaged in the T4 pseudocapsids. Hong et al. further showed that the fusion protein was processed by the T4 gp21 proteinase at specific cleavage sites, inherent within the β-globin gene. The complete process, including expression of the fusion protein, packaging and processing was accomplished in the *E. coli* cells *in vivo*. Analysis of expression of the fusion protein and of processing was performed on bacterial lysates. Packaging of β-globin in the T4 pseudocapsids was analyzed on phages isolated from *E. coli*.

However, Hong et al. is not relevant in any way whatsoever to the subject invention because the subject invention relates to use in the mammalian virus SV40, while the work of Hong et al. describes the use of bacteriophage T4. T4 and SV40 are two widely different viruses. T4 infects bacteria, SV40 infect mammalian cells. The structure of tail containing T4 is unrelated to that of the icosahedral SV40.

The mechanisms involved in DNA encapsidation are likewise completely different. T4 DNA is linear, about 20 times larger than the circular SV40. In T4, DNA is actively transported by viral proteins into the head, and the mature virus requires tail assembly. No such processes exist in SV40.

In the present invention, the capsid proteins are produced in insect cells and the DNA in *E. coli*. Only then are the capsid proteins, extracted from the insect cells, mixed, *in vitro*, with the DNA that is purified from *E. coli*. Thus packaging is

performed in the test tube and not *in vivo*, as in Hong et al.

The present invention describes the use of the mammalian virus SV40 to package DNA, RNA and proteins or peptides, whereas Hong et al. describe the encapsidation of proteins only. Furthermore, the protein is packaged as a fusion protein with T4 internal protein IPIII, and the fusion protein has to be cleaved, for the protein of interest to be functional.

Thus, Hong et al. teach the encapsidation of a protein as a fusion protein with an internal capsid protein of bacteriophage T4, to be later cleaved to liberate the desired protein. The cleavage is an essential part of the process, without which the desired protein will not be delivered into the infected (bacterial) cells. Cleavage is achieved by T4 gp21 proteinase, which is part of the T4 capsid, where it functions in phage maturation. This mechanism facilitates the process described by Hong et al. SV40 does not contain any protease in its capsid, and its capsid does not undergo maturation via protease action. Therefore Hong et al. does not teach a process which is possible to accomplish in SV40 capsids.

Hong *et al.* also does not remedy the deficiencies of Hellwig et al., because for the reasons detailed above, it would not have been obvious for one of ordinary skill in the art at the time the invention was made to modify the particle produced by Hellwig et al. with the viral capsid used for protecting the exogenous protein of Hong et al. The Examiner states that one

of skill in the art would have been motivated to modify the teaching of Hellwig et al. with the teachings of Hong et al. for the expected benefit of packaging non-viral nucleic acids as well as proteins for delivery into the cells of Hellwig et al. Applicants respectfully disagree. The constructs of Hong et al. would not have infected the mammalian cells of Hellwig et al. as explained above.

There would not have been any reasonable expectation of success, firstly because as explained above in great detail, Hellwig et al. itself is not enabling, and provides no reasonable expectation of success, and Hong *et al.* provide no remedy, because they are concerned with a completely different system, a bacteriophage system which is not suitable for infecting mammalian cells. Moreover, the formation of a fusion protein, the desired part of which needs to be cleaved off, in order to obtain a therapeutic product, as claimed in the present invention, is cumbersome and inconvenient, and, furthermore, can cause serious complications in the process of therapy, because of the introduction of unnecessary sequences to the infected cell. In contrast, with the infectious particle complex of the invention, no modifications of the packaged constituent are required.

To support a case of <u>prima facie</u> obviousness, Hellwig et al. and Hong et al., when combined, would have to teach or suggest all elements of the rejected claims. Moreover, there would have to have been a motive to combine them, and a reasonable expectation

of the invention=s success at the time of the invention. This they fail to do.

Thus, Hellwig et al. in view of Hong et al. do not teach or suggest an infectious particle complex and method for preparing such infectious particle complex in which the exogenous constituent is an exogenous protein or peptide, and thus do not teach or suggest all elements of the rejected claims. The Examiner failed to show how these references, alone or combined with others, would motivate one to arrive at the claimed invention, and reasonably expect its success.

Accordingly, the Examiner has failed to establish the prima facie obviousness of claims 12, 29-34 and 47 over these references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over Hellwig et al. in view of Hong et al.

In view of the above remarks, applicants maintain that claims 12, 29-34 and 47 satisfy the requirements of 35 U.S.C. ∋103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in

condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $475.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

10/9/03

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